

Requested Patent EP0038536A1

Title:

ANTI-INFLAMMATORY 4,5-DIARYL- ALPHA
-(POLYFLUOROALKYL)-1H-PYRROLE-2-METHANAMINES

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ABSTRACT:

4,5-Diaryl- alpha -(polyfluoroalkyl)-1H-pyrrole-2-methanamines such as 4,5-bis(4-fluorophenyl)-
alpha alpha -bis-(trifluoromethyl)-1H-pyrrole-2-methanamine, useful in treatment of inflammation.

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(54) **Antinflammatory 4,5-diaryl- α -(polyfluoroalkyl)-1H-pyrrole-2-methanamines.**

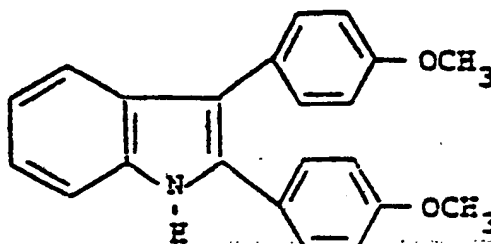
(57) **4,5-Diaryl- α -(polyfluoroalkyl)-1H-pyrrole-2-methanamines such as 4,5-bis(4-fluorophenyl)- α , α -bis-(trifluoromethyl)-1H-pyrrole-2-methanamine, useful in treatment of inflammation.**

Title BP-6181-A
Antiinflammatory 4,5-Diaryl- α -(polyfluoro-
alkyl)-1H-pyrrole-2-methanamines

Background of the Invention

5 This invention relates to antiinflammatory pyrroles.

J. Szmuszkovicz et al., J. Med. Chem., 9, 527 (1966) describe synthesis and biological activity of a clinically tested antiinflammatory agent of the formula



15 Yoshida et al., U.S. Patent 3,709,906 disclose 5-alkyl-2,3-diphenylpyrrole derivatives which are useful as antiinflammatory agents.

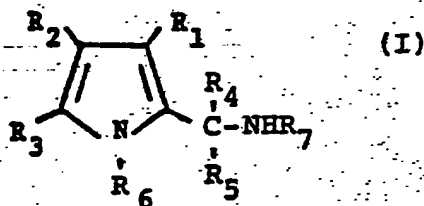
20 There is a continuing need for safe and effective antiinflammatory agents. Inflammation is a disease process characterized by redness, fever, swelling, and pain. Arthritis, in its various forms, is the most prevalent, chronic, and severe of the inflammatory diseases. Traumatic injury and infection also involve inflammation, and antiinflammatory drugs are often used in their treatment. The usefulness of most commercial antiinflammatories is limited because of toxicity and adverse side-effects. Many produce gastric irritation and other effects, such as changes in blood cells and central nervous system. Adreno-cortical steroids produce gastric irritation and suppression of normal adrenal function.

The present invention results from efforts to develop new anti-arthritic compounds with good antiinflammatory activity and minimal side effects that could be more effective in treating arthritis than presently available drugs.

In addition to antiinflammatory properties, some compounds of this invention have demonstrated analgesic activity in a test procedure. This additional property is desirable in treatment of arthritis or related diseases; however, such compounds can be employed solely to alleviate pain.

Summary of the Invention

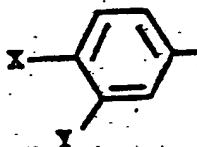
This invention relates to compounds of Formula I, pharmaceutical compositions containing them, and methods of use of these compounds to treat arthritis.



25 wherein

$R_1 = \text{H or } C_1-C_2 \text{ alkyl;}$

R_2 and R_3 independently = 3-pyridyl
or



where

X = H, F, Cl, Br, C₁-C₂ alkyl, C₁-C₂ alkoxy, di(C₁-C₂ alkyl)amino or CH₃S(O)_n where n = 0, 1 or 2; and

Y = H, F or Cl;

5 with the proviso that when Y is F or Cl, then X is F or Cl;

R₄ and R₅ independently = H, CF₃, CF₂H, CF₂Cl, CFCl₂ or CF₂CF₃, with the proviso that no more than one of R₄ and R₅ can be H; and the further proviso that no more than one of R₄ and R₅ can be CF₂CF₃;

10 R₆ and R₇ independently = H, C₁-C₆ alkyl, benzyl or benzyl substituted with up to two atoms selected from the group consisting of F, Cl, Br, NO₂, and CF₃; with the proviso that when R₄ or R₅ is H, then R₇ must be H also; or

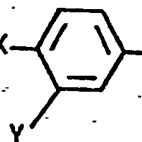
15 a pharmaceutically suitable acid addition salt thereof.

Preferred Compounds

Preferred compounds for utility considerations or ease of synthesis are those in which, independently:

(a) R₁ = H or CH₃; or

25 (b) R₂ and R₃ independently = X-



where X = Br, Cl, F, CH₃O or (CH₃)₂N and Y = H; or

30 (c) R₄ and R₅ = CF₃; or

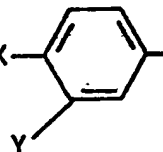
(d) R₆ = H or CH₃; or

(e) R₇ = H or CH₃.

More preferred compounds for the same reasons are those in which:

$R_1 = \text{H or } \text{CH}_3$; and

R_2 and R_3 independently = X-



where $X = \text{Br, Cl, F, CH}_3\text{O or } (\text{CH}_3)_2\text{N}$ and

$Y = \text{H}$; and

R_4 and $R_5 = \text{CF}_3$; and

$R_6 = \text{H or } \text{CH}_3$; and

$R_7 = \text{H or } \text{CH}_3$.

Specifically preferred for the same reasons are:

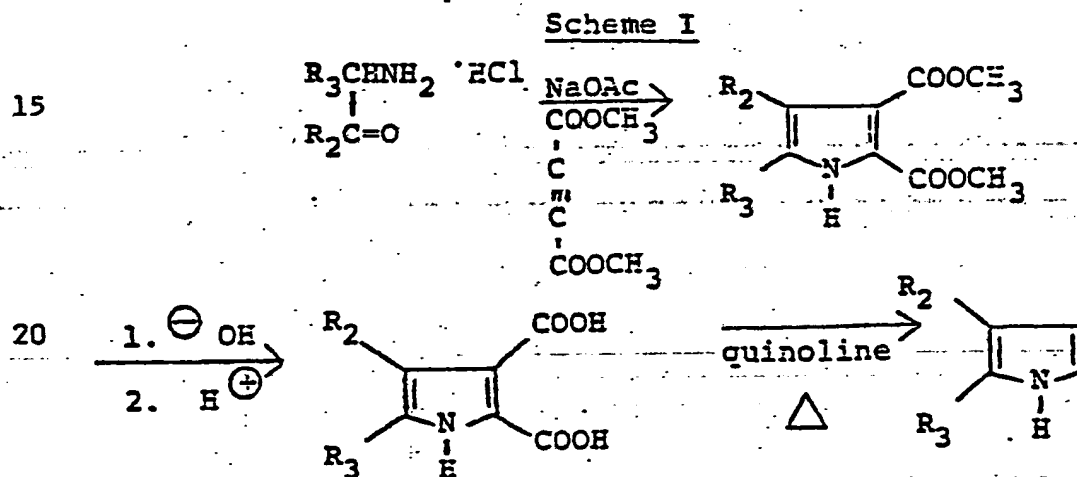
(a) 4,5-Bis(4-fluorophenyl)- α,α -di(trifluoromethyl)-1H-pyrrole-2-methanamine;

(b) 4,5-Bis(4-fluorophenyl)-N-methyl- α,α -di(trifluoromethyl)-1H-pyrrole-2-methanamine; and

(c) 4,5-Bis(4-fluorophenyl)-N,1-dimethyl- α,α -di(trifluoromethyl)-1H-pyrrole-2-methanamine.

Synthesis

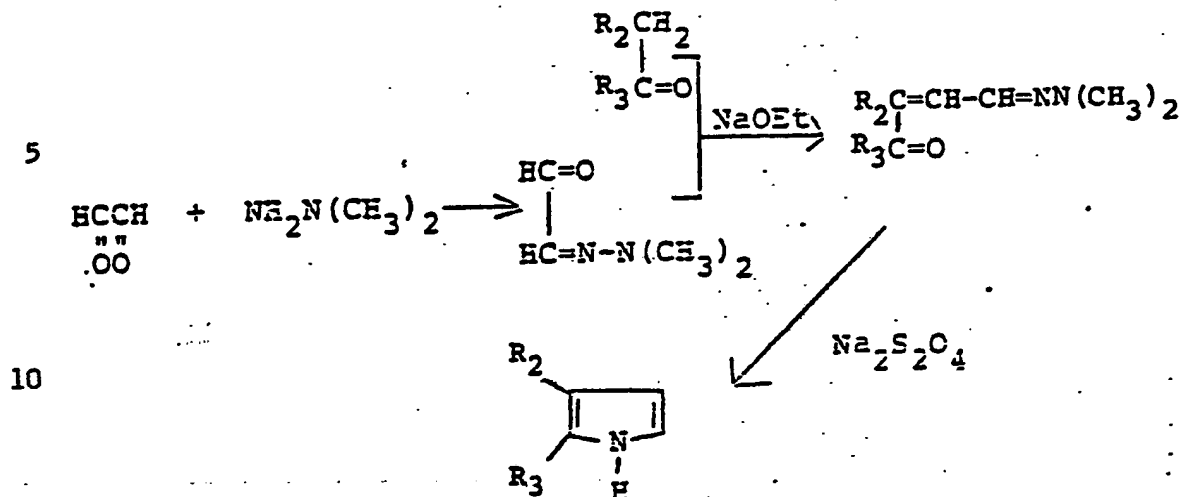
The compounds of this invention can be prepared from 2,3-diarylpyrroles. One method of preparation of 2,3-diarylpyrroles involves reaction of substituted α -aminodeoxybenzoins with acetylene diesters, followed by hydrolysis and decarboxylation according to the procedure used by J. Szmuszkovicz et al., *J. Med. Chem.*, 9, 527 (1966) and by U.S. Patent 3,462,451, the disclosures of which are hereby incorporated by reference, for the synthesis of 2,3-bis(4-methoxyphenyl)pyrrole. (Scheme I).



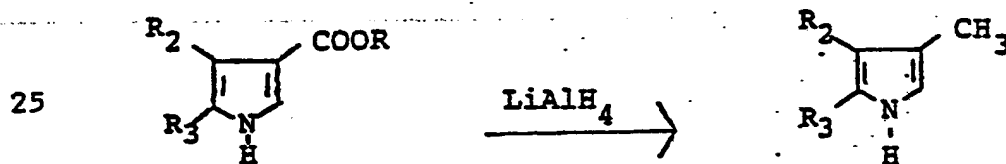
Another method of preparation of 2,3-diarylpyrroles is a modification of the procedure of T. Severin and H. Poehlmann, *Chem. Ber.*, 110, 491 (1977), hereby incorporated by reference, which describes the preparation of monoaryl pyrroles. By using substituted desoxybenzoins, the desired 2,3-diarylpyrroles are formed (Scheme II).

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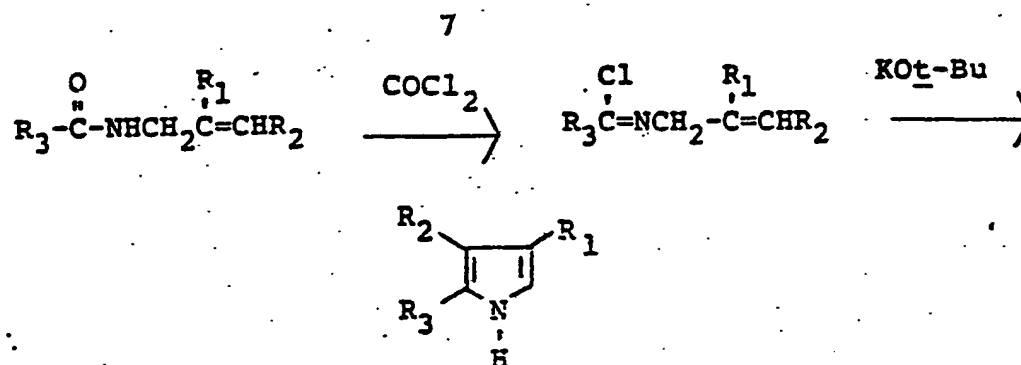
Scheme II



Preparation of 2,3-diaryl-4-alkylpyrroles
 15 can be accomplished by several methods. First,
 4,5-diarylpyrrole-3-carboxylate esters, prepared,
 for instance, by the method of A. M. van Leusen
 et al., Tet. Letters, 5337 (1972) can be reduced
 to the 2,3-diaryl-4-methylpyrroles by lithium
 20 aluminum hydride [following the general procedure
 of R. L. Hinman and S. Theodoropoulos, J. Org. Chem.,
28, 3052 (1963)], hereby incorporated by reference.

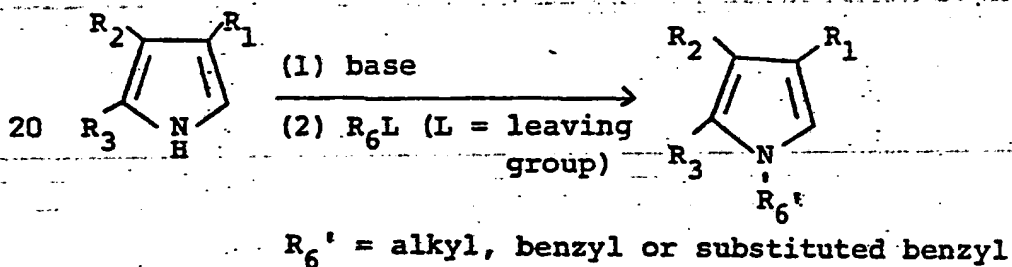


Secondly, 2,3-diaryl-4-alkylpyrroles can be
 prepared by the general procedure of N. Engel and
 30 W. Steglich, Angew. Chem. Int. Ed. Engl., 17, 676
 (1978), hereby incorporated by reference, from
 N-allylcarboxamides.



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1-Alkyl-2,3-diarylpyrroles can be prepared from the corresponding 2,3-diarylpyrroles by treatment with a strong base, such as sodium hydride, followed by alkylation using an alkyl halide, or other suitable
15 alkylating reagent, such as methyl iodide,

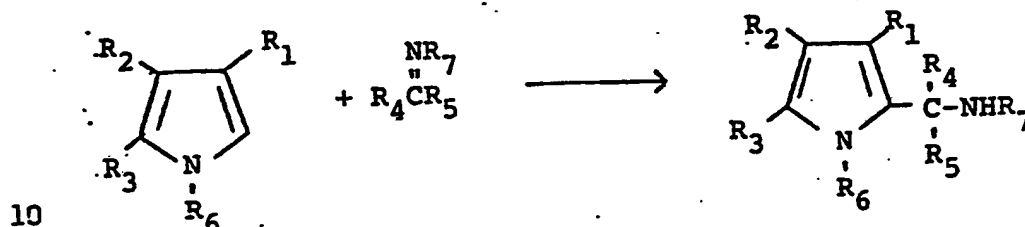


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Introduction of the α,α -bis(polyfluoroalkyl)methanamine group is accomplished by reaction of the 2,3-diarylpyrrole with a fluorinated ketone imine, such as hexafluoroacetone imine. This reaction can be conducted in an inert solvent, such

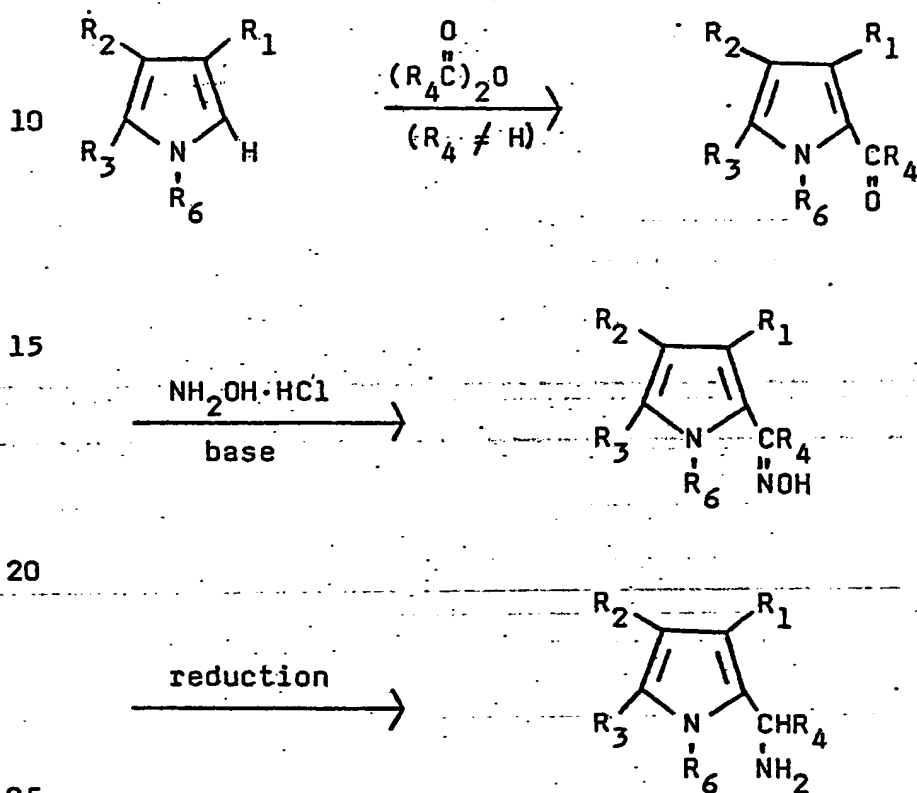


as toluene, at temperatures from ambient to the reflux temperature of the solvent. Acidic catalysts such as AlCl_3 , BF_3 , *p*-toluenesulfonic acid, trifluoroacetic acid or the like are employed to increase the reaction rate. Reaction times are usually from less than one hour to 24 hours. The use of hexafluoroacetone imine in toluene at ambient temperature with catalytic amounts of trifluoroacetic acid or aluminum chloride is preferred. When the polyfluorinated ketone imine employed is substituted on nitrogen by an R_7 group (other than H), this reaction gives rise directly to the corresponding substituted 4,5-diaryl- α,α -(polyfluoroalkyl)-1H-pyrrole-2-methanamines (R_7 = alkyl, benzyl or substituted benzyl).

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Compounds in which one of R_4 and R_5 is H can be prepared by reduction of the oximes, which are in turn prepared by reaction of the corresponding 1-(4,5-diaryl-1H-pyrrol-2-yl)polyfluoroalkanones with hydroxylamine.

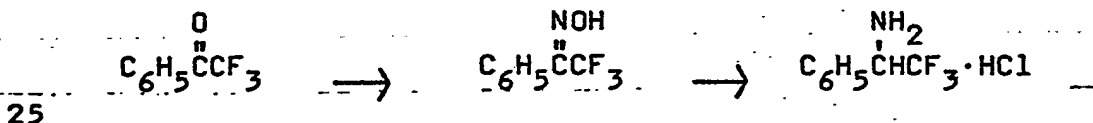


Thus, the 1-(4,5-diaryl-1H-pyrrol-2-yl)-polyfluoro-1-alkanones can be prepared from the corresponding 2,3-diarylpyrroles by treatment with a polyfluorinated acid anhydride in the absence or presence
 5 of a base, such as N,N-dimethylaniline. The reaction can be run in any solvent which is inert to the reactants, at temperatures from -78° to the boiling point of the solvent, preferably at 0°C.

The preparation of the oximes is carried out by
 10 heating the polyfluoroalkanone in the presence of hydroxylamine hydrochloride and a base (such as an alkali metal acetate or alkoxide) in a polar solvent such as ethanol.

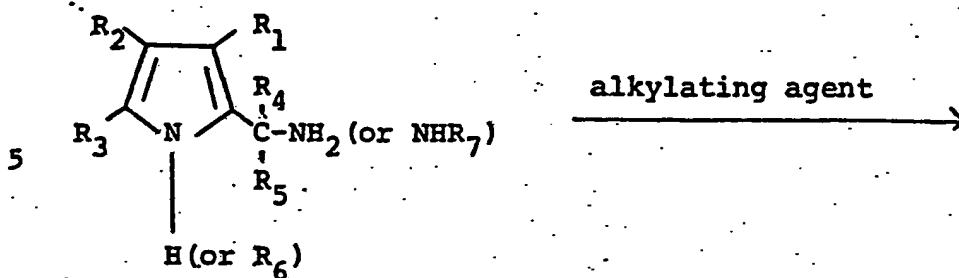
The reduction of the oxime is carried out by
 15 catalytic hydrogenation or by metal hydride reduction. Preferred conditions involve the use of lithium aluminum hydride in an ether solvent, such as diethyl ether or tetrahydrofuran at room temperature.

A similar procedure used in the preparation of
 20 1-phenyl-2,2,2-trifluoroethylamine hydrochloride has been described in the literature [R. A. Shepard and S. E. Wentworth, *J. Org. Chem.*, **32**, 3197 (1967)].

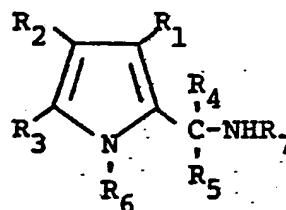


Compounds of Formula I of this invention with
 R₆ and/or R₇ ≠ H can alternatively be prepared by
 alkylation of the corresponding compounds with R₆
 and/or R₇ = H. Alkylation can occur on either or
 30 both of the NH₂ or NH functionalities, depending on the conditions of the reaction. Often mixtures of alkylated products are obtained. These alkylations can be conducted in the presence or absence of a base, such as potassium carbonate,

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15 pyridine, triethylamine, potassium-*t*-butoxide, sodium hydride or the like. Examples of alkylating agents are methyl iodide and benzyl bromide.

20 Pharmaceutically suitable salts of the compounds of Formula I can be prepared by treatment of the free base I with the appropriate acid.

In the following examples, all parts are by weight and temperatures are in degrees centigrade unless otherwise specified.

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Preparation 12,3-Diphenylpyrrole (Method A)A. Dimethyl 4,5-diphenylpyrrole-2,3-dicarboxylate

In a 2 l RB 3-neck flask with mechanical stirrer
5 and condenser was placed 76.7 g (0.31 mole) of desyl
amine hydrochloride [Pschorr et al, Chem. Ber., 35,
2740 (1902)], 750 ml methanol, 88 g (0.62 mole)
dimethyl acetylenedicarboxylate (freshly distilled) and
61 g (0.75 mole) anhydrous sodium acetate. The mixture
10 was heated at reflux for two hours. Then another 44 g
(0.31 mole) of dimethyl acetylenedicarboxylate was
added, and heating continued another two hours. While
the reaction mixture was still at reflux, concentrated
hydrochloric acid (~60 ml, to pH ~2) was added dropwise.
15 The mixture was heated at reflux another hour, then
poured into 2 l water containing 200 ml 10% sodium
bicarbonate solution. With stirring, more sodium
bicarbonate was added until the solution was neutral.
The gummy solid which precipitated was collected and
20 washed with water. Trituration of this gummy material
with ~500 ml of 50% aqueous ethanol gave a tan powdery
solid, which was recrystallized from ~25% aqueous
ethanol to give 65.5 g (63%) of white crystals, m.p. —
25 191-2° [Lit. m.p. 185-7°; J. B. Hendrickson et al,
J. Am. Chem. Soc., 86, 107 (1964)].

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B. 4,5-Diphenylpyrrole-2,3-dicarboxylic Acid

To a mixture of 57.5 g (0.172 mole) of dimethyl 4,5-diphenylpyrrole-2,3-dicarboxylate in 350 ml methanol was added a solution of 71 g (1.78 mole) of sodium hydroxide in 350 ml water. The mixture was heated at reflux for two hours, then cooled in an ice bath. The insoluble white crystals were collected and washed with cold methanol to give the bis sodium salt of the product. The still damp solid was dissolved in 1 l cold water and acidified with conc. hydrochloric acid. The precipitated product was collected by filtration, washed with water containing ~1% hydrochloric acid, then air dried and finally dried in a vacuum oven at 100° to give 50.0 g (95%) of white solid, m.p. 215-218° (dec., depends on heating rate).

C. 2,3-Diphenylpyrrole (Method A)

A mixture of 20 g (0.065 mole) of 4,5-diphenylpyrrole-2,3-dicarboxylic acid in 80 ml quinoline was heated at reflux in an oil bath (bath ~230°) until gas evolution stopped (approx. one-half hour). The reaction mixture was cooled and most of the quinoline was removed by distillation (bp 58° @ 0.2 mm). The partially crystalline residue was chromatographed on 300 g Silic AR CC-7, eluting with toluene to give 12 g (85%) of faintly pink 2,3-diphenylpyrrole which could be further purified by recrystallization from ethanol/water or by sublimation (~125° @ 0.2 mm) to give white solid, m.p. 132-3°.

Anal. Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.98;
N, 6.39.

Found: C, 87.99; H, 5.86;
N, 6.50.

Preparation 22,3-Diphenylpyrrole (Method B)

A. Glyoxal mono(dimethylhydrazone) was prepared by the procedure of T. Severin and H. Poehlmann, Chem. Ber.,
5 110, 491 (1977) to give 36.1 g (80%) of pale yellow liquid, bp 109° (22 mm); lit. bp 90° (16 mm).

B. 4-Dimethylhydrazono-1,2-diphenyl-2-buten-1-one

To a mixture of 19.6 g (0.1 mole) desoxybenzoin
10 and 10 g (0.1 mole) of glyoxal mono(dimethylhydrazone) in 100 ml ethanol was added dropwise a solution of sodium ethoxide prepared by dissolving 2.3 g (0.1 mole) sodium metal in 100 ml ethanol. The mixture was heated at reflux for one-half hour. TLC (90/10, toluene/ethyl
15 acetate) showed a small amount of starting desoxybenzoin, so 2.0 g (0.02 mole) of additional glyoxal mono(dimethylhydrazone) was added. Heating was continued another two hours. TLC at this time showed no starting material, and two clean close yellow product spots (isomers). The
20 mixture was poured into 1 l ice water then extracted with methylene chloride. The organic extracts were dried and concentrated on a rotary evaporator to give 28.7 g (100%) of yellow oil. The NMR showed the presence of two major
25 $N(CH_3)_2$ containing materials (product isomers). The crude oil crystallized from isopropanol to give one pure isomer of product, 13.4 g (48%), pale yellow crystals, m.p. 131-2°.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52;
30 N, 10.06.

Found: C, 77.44; H, 6.46;
N, 10.17.

C. 2,3-Diphenylpyrrole (Method B)

A mixture of 3.1 g (0.011 mole) of 4-dimethyl-hydrazono-1,2-diphenyl-2-buten-1-one, 11.2 g (0.064 mole) sodium hydrosulfite in 75 ml ethanol and 37.5 ml
5 water was heated at reflux for three hours. The mixture was cooled and poured into 300 ml ice water. The white crystalline produce was collected, washed with water and air dried to give 1.9 g (79%), m.p. 130-1°, identical to product obtained via the decarboxy-
10 lation, Method A.

Preparation 32,3-Diphenyl-4-methylpyrrole

A. Ethyl 4,5-diphenylpyrrole-3-carboxylate was prepared by a procedure similar to that used by A. M. van Leusen et al., Tet. Letters, 5337 (1972) for the
15 preparation of the methyl ester. The ethyl ester was obtained as a white solid, m.p. 207-208.5° (methyl cyclohexane/toluene).

20 Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81.

Found: C, 77.92; H, 5.87;
77.90 5.88

N, 4.60.
4.62.

25 B. 2,3-Diphenyl-4-methylpyrrole

To a stirred slurry of 0.76 g (20 mmoles) of lithium aluminum hydride in 25 ml THF was added dropwise a solution of 0.58 g (2 mmoles) of ethyl
30 4,5-diphenylpyrrole-3-carboxylate in 5 ml THF. The mixture was heated at reflux overnight. After cooling, 0.8 ml water, 2.4 ml 15% sodium hydroxide solution and 0.8 ml water were added dropwise. The solids were removed by filtration and the filtrate concentrated by
35 rotary evaporation. The crystalline residue was purified by chromatography on 50 g silicic acid (CC-F),

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eluting with hexane/toluene (90/10) to give 0.25 g of product, m.p. 163-4°.

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48;
N, 6.00.

Found: C, 87.77; H, 6.60;

N, 5.89.

Preparation 4

2,3-Bis(4-fluorophenyl)-4-methyl-1H-pyrrole

A. 3-(4-Fluorophenyl)-2-methyl-2-propen-1-al

10 To a solution of 124 g (1 mole) of 4-fluorobenzaldehyde and 8 g (0.143 mole) of potassium hydroxide in 500 ml ethanol at room temperature was added dropwise a solution of 52.2 g (0.9 mole) of propionaldehyde in 100 ml ethanol. After stirring
15 for 0.5 hour, the mixture was acidified with acetic acid and concentrated by rotary evaporation. The residue was partitioned between methylene chloride and water. The aqueous layer was extracted three times with additional methylene chloride. The combined
20 organic layers were dried and concentrated. Distillation through a 12-inch vacuum jacketed column gave 113.5 g (77 %) of pale yellow low-melting crystalline product, b.p. 70-72°C (0.4-0.7 mm).

Anal. Calcd. for $C_{10}H_9FO$: C, 73.16; H, 5.53

Found: C, 72.89, 72.72;

H, 5.66, 5.46.

B. 3-(4-Fluorophenyl)-2-methyl-2-propen-1-ol

To a solution of 113 g (0.69 mole) of 3-(4-fluorophenyl)-2-methyl-2-propen-1-al in 800 ml ethanol at
30 10°C was added in portions 13.1 g (0.345 mole) of sodium borohydride. After the addition was complete, the reaction mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath while 35 350 ml of 1N hydrochloric acid was added dropwise to give a final pH of ~7. The mixture was diluted

with 500 ml water and extracted three times with methylene chloride. The organic extracts were dried and concentrated and the residue distilled to give 56.1 g (49%) of colorless liquid, b.p. 68-70°C (0.15 mm).

5 Anal. Calcd. for $C_{10}H_{11}FO$: C, 72.27; H, 6.67

Found: C, 72.30, 72.38;

H, 6.61, 6.62.

C. 1-Chloro-3-(4-fluorophenyl)-2-methyl-2-propene

To a solution of 53.6 g (0.32 mole) of 3-(4-fluorophenyl)-2-methyl-2-propen-1-ol in 100 ml methylene chloride was added dropwise a solution of 57.1 g (0.48 mole) of thionyl chloride in 100 ml methylene chloride. The reaction mixture was stirred at room temperature for 2 hours, then concentrated by rotary evaporation. The product was checked by NMR, then used crude in the reaction with ammonia.

D. 3-(4-Fluorophenyl)-2-methyl-2-propen-1-amine

A quantity of 59.1 g (0.32 mole) of 1-chloro-3-(4-fluorophenyl)-2-methyl-2-propene and 500 ml ethanol was loaded in a pressure vessel. The vessel was cool-evacuated and 100 g of ammonia was added. The mixture was heated at 95° for 3 hours with shaking. The vessel was cooled, vented and the contents rinsed out with ethanol. The mixture was concentrated by rotary evaporation. The residue was diluted with 1.5 l water and acidified with concentrated hydrochloric acid. This mixture was filtered to remove some insoluble solid (undissolved amine hydrochloride). The aqueous filtrate was extracted with ether to remove any non-basic impurities. The aqueous layer was combined with the insoluble solid and made basic with 5% sodium hydroxide solution. This was then extracted with ether and the ether extracts were dried and concentrated. Distillation of the residue gave 22.8 g (43%) of colorless liquid, b.p. 57°C (0.2 mm).

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Anal. Calcd. for $C_{10}H_{12}FN$: C, 72.70; H, 7.32;
 N, 8.48

Found: C, 72.67, 72.59;
 H, 7.48, 7.53
 N, 8.31.

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E. 4-Fluoro-N-[3-(4-fluorophenyl)-2-methyl-2-propenyl]benzamide

To a vigorously stirred mixture of 19.8 g
 10 (0.12 mole) of 3-(4-fluorophenyl)-2-methyl-2-propen-1-amine and 30.2 g (0.36 mole) of sodium bicarbonate in 500 ml water at 5°C was added dropwise 22.2 g (0.14 mole) of 4-fluorobenzoyl chloride. The mixture was stirred another 3 hours at 5°C
 15 then at room temperature overnight. The white solid which had formed was collected, washed with saturated sodium bicarbonate solution, then with water, then with hexane, then air dried to give 33.4 g (97%) of product, m.p. 107-109°C.

20 Anal. Calcd. for $C_{17}H_{15}F_2NO$: C, 71.07; H, 5.26
 N, 4.88

Found: C, 70.85; H, 5.48;
 N, 4.70.

F. 2,3-Bis(4-fluorophenyl)-4-methyl-1H-pyrrole

Using the general procedure of N. Engel and
 25 W. Steglich, Angew. Chem. Int. Ed. Engl., 17, 676 (1978), to a slurry at room temperature of 28.7 g (0.1 mole) of 4-fluoro-N-[3-(4-fluorophenyl)-2-methyl-2-propenyl]benzamide in 100 ml toluene containing 1 ml
 30 DMF, stirred under nitrogen, with a dry ice condenser attached, was added dropwise a solution of 39.6 g (28.3 ml, 0.4 mole) of phosgene in 100 ml toluene. The mixture was warmed slightly with a heat gun, then stirred at room temperature overnight. The solution
 35 was concentrated by rotary evaporation to give a yellow oil. This was dissolved in 100 ml dry THF

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(small amount of insoluble solid removed by decanting the solution) and the solution was added dropwise to a cool (15°) solution of 33.5 g (0.3 mole) of potassium t-butoxide in 150 ml DMSO. The dark purple solution was stirred at ~20°C for 1 hour, then was poured into 1 liter ice water. This was extracted with ether and the ether layers backwashed with water. The ether layer was dried and concentrated and the residue was chromatographed on 900 g of silica gel, eluting with hexane containing 10-40% toluene, to give, after recrystallization from methyl cyclohexane, 10.8 g (40%) of white product, m.p. 126-7°C.

Anal. Calcd. for $C_{17}H_{13}F_2N$: C, 75.82; H, 4.87;
N, 5.20

Found: C, 75.87; H, 4.85;
N, 5.13.

Preparation 5

2,3-bis(4-Fluorophenyl)-1-methyl-1H-pyrrole

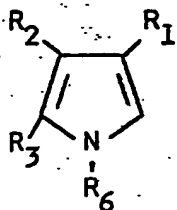
To a mixture of 1.5 g (0.038 mole) of 60% sodium hydride dispersion and 100 ml DMSO was added dropwise a solution of 5.1 g (0.02 mole) of 2,3-bis(4-fluorophenyl)-1H-pyrrole in 25 ml DMSO. After the mixture was stirred one hour at room temperature, 5.6 g (0.04 mole) of methyl iodide was added dropwise. The mixture was stirred at room temperature overnight, then poured into water and extracted with ether. The ether extracts were backwashed with water three times, then dried and concentrated. The crude solid was recrystallized from hexane to give 4.3 g of product, m.p. 129-129.5°.

Anal. Calcd. for $C_{17}H_{13}F_2N$: C, 75.82; H, 4.87;
N, 5.20

Found: C, 75.89, 75.78;
H, 4.98, 4.97;
N, 5.18, 5.10.

Other 2,3-diarylpyrroles prepared by these procedures are given in Table I.

Table I
2,3-Diarylpyrroles



	<u>Prep.</u>	<u>R₂</u>	<u>R₃</u>	<u>R₁</u>	<u>R₆</u>	<u>m.p. °C</u>	<u>Yield (%)</u>
15	6	4-ClC ₆ H ₄	4-ClC ₆ H ₄	H	H	124-127	70
	7	4-FC ₆ H ₄	4-FC ₆ H ₄	H	H	119.5-120.5	80
	8	C ₆ H ₅	3,4-diClC ₆ H ₃	H	H	112-113	28
	9	4-FC ₆ H ₄	4-BrC ₆ H ₄	H	H	129-130	69
	10	C ₆ H ₅	3-pyridyl	H	H	190-192	23
20	11	4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	H	H	oil	64
	12	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	H	H	128-129	83
	13	4-FC ₆ H ₄	4-(CH ₃) ₂ NC ₆ H ₄	H	H	200-201	47
	14	4-FC ₆ H ₄	3-pyridyl	H	H	173-174	17
	15	4-FC ₆ H ₄	4-CH ₃ SC ₆ H ₄	H	H	164-165	71
25	16	4-FC ₆ H ₄	4-CH ₃ SO ₂ C ₆ H ₄	H	H	268-270	48
	17	4-FC ₆ H ₄	4-FC ₆ H ₄	H	CH ₂ C ₆ H ₅	118-119	35

30

35

Example 14,5-Bis(4-fluorophenyl)- α,α -bis(trifluoromethyl)-
1H-pyrrole-2-methanamine

A mixture of 3.85 g (0.015 mole) of 2,3-bis-
5 (4-fluorophenyl)-1H-pyrrole and 3.0 g (0.018
mole) of hexafluoroisopropylidenimine in 75 ml
toluene was stirred at room temperature under a
dry ice condenser for one hour, then heated at
reflux for one hour. Since TLC indicated little
10 reaction, a quantity of 0.1 g of aluminum chloride
was added to the cooled reaction mixture. The
mixture was stirred at room temperature overnight.
An additional quantity of 1.0 g (0.006 mole)
of hexafluoroisopropylidenimine was added in
15 1 ml of cold toluene and, after two hours at
room temperature, another 0.1 g of aluminum
chloride was added. The mixture was stirred
at room temperature overnight, then concentrated
by rotary evaporation. The residue was chromato-
20 graphed on silica gel, eluting with toluene/
hexane mixtures, to give, after recrystallization
from hexane, 4.6 g of product, m.p. 88-89°.

Anal. Calcd. for $C_{19}H_{12}F_8N_2$: C, 54.30; H, 2.88;
N, 6.67.

25 Found: C, 54.25; H, 2.86;
N, 6.51.

30

35

Example 24,5-Bis(4-fluorophenyl)- α -(trifluoromethyl)-1H-pyrrole-2-methanamine5 A. 1-[4,5-Bis(4-fluorophenyl)-1H-pyrrol-2-yl]-2,2,2-trifluoroethanone

To a solution of 2.5 g (0.012 mole) of trifluoroacetic anhydride in 30 ml ether at 0° was added dropwise a solution of 2.6 g (0.01 mole) of 2,3-bis(4-fluorophenyl)-1H-pyrrole and 1.5 g (0.012 mole) of
10 N,N-dimethylaniline in 20 ml ether. The reaction mixture was stirred at 0° for 1.5 hours, then diluted with more ether, washed successively with water, 1N hydrochloric acid, then water again. The organic layer was dried and concentrated and the residue was
15 purified by chromatography on silica gel, eluting with toluene, to give 2.7 g of white product, m.p. 211-212° (recrystallized from methyl cyclohexane/toluene).

Anal. Calcd. for $C_{18}H_{10}F_5NO$: C, 61.55; H, 2.87;
N, 3.99

20

Found: C, 61.65; H, 3.13;
N, 3.52.

B. 1-[4,5-Bis(4-fluorophenyl)-1H-pyrrol-2-yl]-2,2,2-trifluoroethanone, Oxime

A mixture of 0.42 g (6 mmoles) of hydroxylamine
25 hydrochloride, 0.3 g (6 mmoles) of sodium methoxide and 1.05 g (3 mmoles) of the product from part A in 50 ml ethanol was heated at reflux overnight. An additional quantity of hydroxylamine, prepared from 0.42 g of hydroxylamine and 0.3 g of sodium methoxide, was
30 added and heating was continued another three days. Another batch of hydroxylamine was added and heating continued overnight. This was repeated again, then the reaction mixture was poured into water and the white solid precipitate was collected and washed with
35 water. Chromatography on silica gel, eluting with a

solvent containing 75% to 100% toluene and 25% to 0% hexane, gave 0.5 g of the oxime as a white solid, m.p. 215-216° (recrystallized from methyl cyclohexane/toluene).

5 Anal. Calcd. for $C_{18}H_{11}F_5N_2O$: C, 59.02; H, 3.03; N, 7.65.

Found: C, 59.00; 59.07;

H, 3.06, 3.13;

N, 7.65, 7.62.

10

C. 4,5-Bis(4-fluorophenyl)- α,α -(trifluoromethyl)-1H-pyrrole-2-methanamine

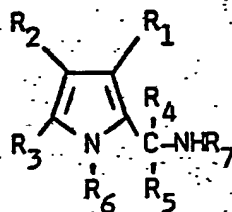
To a stirred mixture of 0.8 g (0.02 mole) of lithium aluminum hydride in 50 ml ether was added
15 dropwise a solution of 3.7 g of the oxime from part B in 50 ml ether. The reaction mixture was stirred overnight at room temperature, then heated at reflux overnight. A quantity of 50 ml dry THF was added and heating at reflux was continued two more days. A
20 solution of 8 g of sodium hydroxide in 15 ml water was added dropwise, then the mixture was diluted with more water and ether. The organic layer was separated after addition of 1N hydrochloric acid to reduce the emulsion. The aqueous layer was extracted with more
25 ether and with methylene chloride. The combined organic layers were dried and concentrated. The crude product was purified by chromatography on silica gel, eluting with toluene:ethyl acetate (90:10) to give 1.1 g of pure product as an oil, which was characterized
30 by TLC, IR, 1H - and ^{19}F -NMR and mass spectrum.

Mass Spectrum: Calcd. for $C_{18}H_{13}F_5N_2$: 352.

Found: 352.

Other 4,5-diaryl- α,α -di(polyfluoroalkyl)-1H-pyrrole-2-methanamines that have been prepared by these proce-
35 dures are given in Table II.

Table II

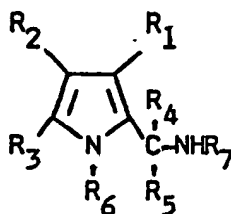


Ex.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	m.p. °C	Yield (%)
3	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₃	H	129-130	75
4	H	4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	CF ₃	CF ₃	H	H	120-120.5	37
5	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	CH ₃	129-130	73
6	H	4-FC ₆ H ₄	4-BrC ₆ H ₄	CF ₃	CF ₃	H	H	125-126	77
7	H	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	CF ₃	CF ₃	H	H	143-144	71
8	CH ₃	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H	154-155	83
9	H	4-FC ₆ H ₄	4-(CH ₃) ₂ NC ₆ H ₄	CF ₃	CF ₃	H	H	155-156	87
10	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	CF ₃	CF ₃	H	H	119-119.5	82
11	H	C ₆ H ₅	C ₆ H ₅	CF ₃	CF ₃	H	H	124-125	90
12	H	4-FC ₆ H ₄	3-pyridyl	CF ₃	CF ₃	H	H	249-250	16
13	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₂ C ₆ H ₅	H	111-111.5	25
14	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₃	CH ₃	110-111	62
15	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₂ Cl	H	H	94-95	5
16	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₂ H	H	H	98-100*	2

*the compound of Example 16 was ~60-70% pure

Following the procedure described, the following 4,5-diaryl- α -(polyfluoroalkyl)-1H-pyrrole-2-methanamines can be prepared (Table III).

Table III



Ex.	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>R₄</u>	<u>R₅</u>	<u>R₆</u>	<u>R₇</u>
17	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₂ Cl	CF ₂ Cl	H	H
15 18	-CH ₂ CH ₃	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H
19	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	-CH ₂ CH ₂ CH ₃	H
20	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	C ₆ H ₁₃ -
21	H	3-F, 4-ClC ₆ H ₃	4-CH ₃ OC ₆ H ₄	CF ₃	CF ₃	H	H
22	CH ₃	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₃	CH ₃
20 23	H	4-FC ₆ H ₄	4-CH ₃ SO ₂ C ₆ H ₄	CF ₃	CF ₃	H	H
24	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CFCl ₂	CF ₂ Cl	H	H
25	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	4-NO ₂ C ₆ H ₄ CH ₂ -	H
26	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	-CH ₂ C ₆ H ₅
27	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₂ CF ₃	H	H
25 28	H	4-FC ₆ H ₄	4-FC ₆ H ₄	H	CF ₂ CF ₃	H	H
29	H	4-C ₂ H ₅ C ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H
30	H	4-C ₂ H ₅ OC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H
31	H	4-(C ₂ H ₅) ₂ NC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H
32	H	4-CH ₃ SC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	C ₆ H ₁₃	H

Dosage Forms

The antiarthritic agents of this invention can be administered to treat arthritis by any means that produces contact of the active agent with the agent's
5 site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals; either as individual therapeutic agents or in a combination of
10 therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic
15 characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active
20 ingredient can be about 0.01 to 40 milligrams per kilogram of body weight. Ordinarily 0.05 to 20, and preferably 0.1 to 4 milligrams per kilogram per day given in divided doses 2 to 4 times a day or in sustained release form is effective to obtain desired results.

25 Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active
30 ingredient will ordinarily be present in an amount of about 0.5 - 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and
35 powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions; it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coating for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, E. W. Martin, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 50 milligrams of powdered active ingredient 175 milligrams of lactose, 24 milligrams of talc, and 6 milligrams magnesium stearate.

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 50 milligrams of the active ingredient. The capsules are washed in petroleum ether and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 50 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 10 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

29

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1% by weight of active ingredient in sodium chloride injection U.S.P. XV and sterilizing by commonly used techniques.

Use

To detect and compare the anti-inflammatory activities of compounds in this series and standard drugs, a test was used based on a standard model of arthritis for which there is good correlation with human efficacy. The model is adjuvant-induced arthritis in rats. Federation Proceedings, Vol. 32, No. 2, 1973, "Models Used for the Study and Therapy of Rheumatoid Arthritis" - Symposium of the American Society for Pharmacology and Experimental Therapeutics - states "The rat polyarthritis produced by intradermal injection of a suspension of Mycobacterium tuberculosis is mineral oil (adjuvant) has been used extensively for the screening of drugs of potential use in rheumatoid arthritis."

Compounds of this invention have shown activity in adjuvant-induced arthritis in rats which is widely recognized as a good model of human rheumatoid arthritis.

METHODSEstablished Adjuvant-Induced Arthritis in Rats

Lewis (Wistar) male rats (Charles River Breeding Laboratories, Wilmington, Mass.) weighing 175-220 grams were injected subcutaneously with 0.1 ml of adjuvant in the plantar area of the right hind paw. The adjuvant was prepared by bead-milling, heat-killed, lyophilized Mycobacterium butyricum (Difco #0640) in light mineral oil (Fisher Scientific Co. #0-119 Paraffin Oil -

Saybolt Viscosity 125/135) 5 mg/ml. Twenty non-arthritic control rats were injected with mineral oil. The animals received water and Wayne Lab-Blox ad libitum*.

The rats were held for 14 days to allow the development of polyarthritis. The volume of the uninjected, left-hind paw of each rat was measured by using a Ugo Basile Volume Differential Meter, Model 7101. Adjuvant injected rats showing no evidence of arthritis were discarded and the arthritic rats were distributed into groups of 10 having equal mean paw volumes with equal standard deviation. Non-arthritic (oil-injected) control rats were distributed to 2 groups of 10. Suspensions of test compounds were prepared for dosing by bead-milling (4 mm glass beads in rubber stoppered serum bottles) for 4-5 hours in aqueous 1% polyvinyl alcohol, 5% gum acacia and 0.5% methylparaben.

Test compounds were given orally by gavage once daily for 7 days (days 14-20). The 2 groups of oil injected, non-arthritic control rats and the 2 groups of arthritic control rats received vehicle only for 7 days. Paw volumes (uninjected left hind paw) were measured 20 hours after the last dose (on day 21).

Percent decrease from control mean paw volume was calculated with the following formula:

$$\frac{\text{Arthritic Vehicle Control Mean Paw Volume (ml)} - \text{Arthritic Treatment Mean Paw Volume (ml)}}{\text{Arthritic Vehicle Control Mean Paw Volume (ml)} - \text{Non-Arthritic Vehicle Control Mean Paw Volume (ml)}} \times 100 =$$

% Decrease from Control Mean Paw Volume

*while on a 10-hour light - 14 hour-dark cycle

Dose-response regression lines of the % decrease were plotted on semi-log paper and the ED_{50} % for decrease from control paw volume was estimated by inspection.

5 Phenylquinone Writhing Test

 The phenylquinone writhing test, modified from Siegmund, et al., Proc. Soc. Exp. Biol. Med., 95, 729 (1957), was employed. A test compound suspended in 1% methylcellulose was given orally to fasted (17-21
10 hours) female white mice, 5-20 animals per double blind test. Aqueous (0.01% phenyl-p-benzoquinone) phenylquinone was injected intraperitoneally 24 minutes later using 0.20 ml per mouse. Commencing
15 at 30 minutes after the oral administration of the test compound, the mice were observed for 10 minutes for a characteristic stretching or writhing syndrome which is indicative of pain induced by phenylquinone. The effective analgesic dose for 50% of the mice
(ED_{50}) was calculated by the moving average method
20 of Thompson, W. R., Bact. Rev., 11, 115-145 (1947).

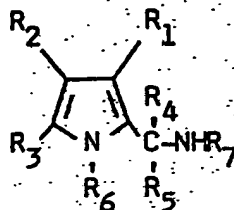
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Results

Table IV
Antiarthritic and Analgesic Activity



Ex.	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>R₄</u>	<u>R₅</u>	<u>R₆</u>	<u>R₇</u>
1	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	H
2	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	H	H	H
15	3	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₃
4	H	4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	CF ₃	CF ₃	H	H
5	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H	CH ₃
6	H	4-FC ₆ H ₄	4-BrC ₆ H ₄	CF ₃	CF ₃	H	H
7	H	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	CF ₃	CF ₃	H	H
20	8	CH ₃	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	H
9	H	4-FC ₆ H ₄	4-(CH ₃) ₂ NC ₆ H ₄	CF ₃	CF ₃	H	H
10	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	CF ₃	CF ₃	H	H
11	H	C ₆ H ₅	C ₆ H ₅	CF ₃	CF ₃	H	H
12	H	4-FC ₆ H ₄	3-pyridyl	CF ₃	CF ₃	H	H
25	13	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₂ C ₆ H ₅
14	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₃	CH ₃	CH ₃
15	H	4-FC ₆ H ₄	4-FC ₆ H ₄	CF ₃	CF ₂ Cl	H	H

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Table IV (continued)

	Ex.	Adjuvant Arthritic ED ₅₀ (mg/kg)	Analgesic Phenylquinone Writhing ED ₅₀ (mg/kg)
5	1	0.45	27
	2	>25(29%)	-
	3	2.6	> 108
	4	3.3	45
10	5	0.8	> 108
	6	3.4	> 108
	7	> 9 (45%)	> 108
	8	0.77	> 108
	9	4.9	> 108
	10	4.4	> 108
15	11	20	> 108
	12	12.5	> 108
	13	>25(24%)	> 108
	14	1.0	> 108
20	15	0.7	-

("___" indicates not tested.)

25

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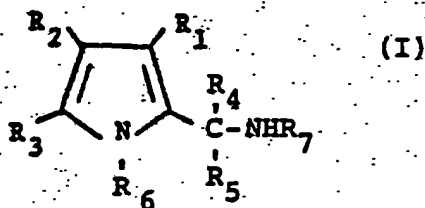
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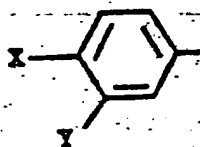
WHAT IS CLAIMED IS:

BP-6181-A

1. A compound of the formula



wherein

10 $R_1 = \text{H or } C_1-C_2 \text{ alkyl;}$ $R_2 \text{ and } R_3 \text{ independently = 3-pyridyl}$
or

where

$X = \text{H, F, Cl, Br, } C_1-C_2 \text{ alkyl, } C_1-C_2$
alkoxy, di(C_1-C_2 alkyl)amino or
 $\text{CH}_3\text{S(O)}_n$ where $n = 0, 1 \text{ or } 2$; and

20 $Y = \text{H, F or Cl;}$ with the proviso that when Y is F or Cl , then
 X is F or Cl ;

25 $R_4 \text{ and } R_5 \text{ independently = H, CF}_3, \text{CF}_2\text{H,}$
 $\text{CF}_2\text{Cl, CFCl}_2 \text{ or CF}_2\text{CF}_3$, with the
proviso that no more than one of R_4 and
 R_5 can be H ; and the further proviso that
no more than one of R_4 and R_5 can be
 CF_2CF_3 ;

30 $R_6 \text{ and } R_7 \text{ independently = H, } C_1-C_6$
alkyl, benzyl or benzyl substituted with up
to two atoms selected from the group con-
sisting of F, Cl, Br, NO_2 , and CF_3 ; with
the proviso that when R_4 or R_5 is H , then
 R_7 must be H also; or

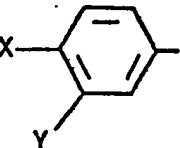
35 a pharmaceutically suitable acid addition salt
thereof.

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2. A compound of Claim 1 where $R_1 = H$ or CH_3 .

3. A compound of Claim 1 where

5

R_2 and R_3 independently = X-

where X = Br, Cl, F, CH_3O or $(CH_3)_2N$ and
Y = H.

10

4. A compound of Claim 1 where R_4 and $R_5 = CF_3$.

CH_3 .

5. A compound of Claim 1 where $R_6 = H$ or

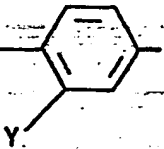
15

CH_3 .

6. A compound of Claim 1 where $R_7 = H$ or

7. A compound of Claim 1 where

$R_1 = H$ or CH_3 ;

R_2 and R_3 independently = X-

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where X = Br, Cl, F, CH_3O or $(CH_3)_2N$ and
Y = H; and

R_4 and $R_5 = CF_3$;

$R_6 = H$ or CH_3 ; and

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$R_7 = H$ or CH_3 .

8. The compounds of claim 1, selected from 4,5-bis-(4-fluorophenyl)- α, α' -di(trifluoromethyl)-1H-pyrrole-2-methanamine, 4,5-bis-(4-fluorophenyl)-N-methyl- α, α' -di(trifluoromethyl)-1H-pyrrole-2-methanamine, and 4,5-bis-(4-fluorophenyl)-N,1-dimethyl- α, α' -di(trifluoromethyl)-1H-pyrrole-2-methanamine.

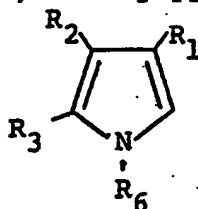
9. A pharmaceutical composition consisting essentially of a suitable pharmaceutical carrier and an effective antiinflammatory amount of a compound of claims 1 - 8.

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10. A process for preparing a compound of Claim 1 which comprises

(a) contacting a 2,3-diarylpyrrole of the formula

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with a polyfluorinated ketone imine $R_4C(R_5)=NR_7$,
 10 where R_1-R_7 are as previously defined (except that R_4 and R_5 cannot equal H), in the absence or presence of a suitable acidic catalyst; and optionally:

(b) when at least one of R_6 and R_7 are H, contacting
 15 the product of step (a) with an alkylating agent; and optionally:

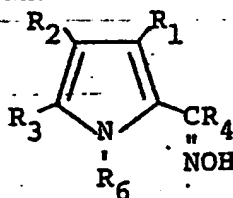
(c) converting the product of step (a) or (b) into a pharmaceutically suitable salt.

20

11. A process for preparing a compound of Claim 1 which comprises

(a) contacting a 1-(4,5-diaryl-1H-pyrrol-2-yl)-polyfluoro-1-alkanone oxime of the formula

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($R_4 \neq H$)

with a reducing agent, and optionally;

(b) contacting the product of step (a) with
 30 an alkylating agent; and optionally,

(c) converting the product of step (a) or (b) into a pharmaceutically suitable salt.

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European Patent
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EUROPEAN SEARCH REPORT

0038536

Application number

EP 81 10 2932

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	FR - A - 2 411 180 (SAGAMI) * Pages 5,6 * --	1,9	C 07 D 207/335 C 07 D 401/04 A 61 K 31/40
	GB - A - 1 247 994 (SANKYO) * Complet. document * --	1,9	
	DE - A - 2 062 985 (T. MESSER-SCHMIDT) * Pages 11,12 * ----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 D 207/335 C 07 D 401/04
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search The Hague	Date of completion of the search 12-06-1981	Examiner MAISONNEUVE	

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